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Review

Hereditary motor and sensory neuropathies: Understanding molecular pathogenesis could lead to future treatment strategies☆

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ABSTRACT

Inherited peripheral neuropathies, like many other degenerative disorders, have been challenging to treat. At this point, there is little specific therapy for the inherited neuropathies other than genetic counseling as well as symptomatic treatment and rehabilitation. In the past, ascorbic acid, progesterone antagonists, and subcutaneous neurotrophin-3 (NT3) injections have demonstrated improvement in animal models of CMT 1A, the most common inherited neuropathy, but have failed to translate any effect in humans. Given the difficulty in treatment, it is important to understand the molecular pathogenesis of hereditary neuropathies in order to strategize potential future therapies. The hereditary neuropathies are in an era of molecular insight and over the past 20 years, more than 78 subtypes of Charcot Marie Tooth disease (CMT) have been identified and extensively studied to understand the biological pathways in greater detail. Next generation molecular sequencing has also improved the diagnosis as well as the understanding of CMT. A greater understanding of the molecular pathways will help pave the way to future therapeutics of CMT. This article is part of a Special Issue entitled: Neuromuscular Diseases: Pathology and Molecular Pathogenesis.

1. Introduction

Inherited peripheral neuropathies, like many other degenerative disorders, have been challenging to treat. At this point, there is little specific therapy for the inherited neuropathies other than genetic counseling as well as symptomatic treatment and rehabilitation. In the past, ascorbic acid, progesterone antagonists, and subcutaneous neurotrophin-3 (NT3) injections have demonstrated improvement in animal models of CMT 1A, the most common inherited neuropathy, but have failed to translate any effect in humans. Given the difficulty in treatment, it is important to understand the molecular pathogenesis of hereditary neuropathies in order to strategize potential future therapies. The hereditary neuropathies are in an era of molecular insight and over the past 20 years, more than 78 subtypes of CMT have been identified and extensively studied to understand the biological pathways in greater detail. Next generation molecular sequencing has also improved the diagnosis as well as the understanding of CMT. A greater understanding of the molecular pathways will help pave the way to future therapeutics of CMT.

2. Background

Inherited neuropathies are some of the most common inherited neurological disorders [1]. Inherited neuropathies not part of another syndrome are named hereditary motor and sensory neuropathy (HMSN) or Charcot Marie Tooth disease (CMT). CMT stands for Charcot Marie Tooth, named after three neurologists who described the condition in 1886 [2]. CMT is the most common inherited disorder of the human peripheral nerve with a prevalence of 1 in 2500 [3]. While CMT is used as a term for hereditary motor and sensory neuropathies, it may also be viewed as a spectrum ranging from the pure motor neuropathies (HMNs) to the predominantly pure sensory neuropathies (HSNs); the following review will focus on hereditary motor and sensory neuropathies.

Over the past 25 years, a dramatic revolution in molecular genetics of inherited neuropathies has occurred. More than 40 genes causing CMT have been identified with many different types of mutations. These mutations provide clues into the cellular pathways of inherited neuropathies and knowledge of cellular pathways can help provide

Abbreviations: CMT, Charcot Marie Tooth disease; AD, Autosomal dominant; AR, Autosomal recessive; MNCV, Motor nerve conduction velocity; CMAP, Compound muscle action potential; PMP22, Peripheral myelin protein 22; HMSN, Hereditary motor sensory neuropathy; LITAF, lipopolysaccharide-induced tumor-necrosis factor (TNF)-alpha factor; HMN, Hereditary motor neuropathy; HSN, Hereditary sensory neuropathy; Cx32, Connexin 32; MPZ, Myelin protein zero; NT3, Neurotrophin-3; INF2, Inverted formin 2; PRX, Periaxin; FGD4, Frabin; LITAF, Lipopolysaccharide-induced tumor necrosis factor-alpha factor; MTMR2, Myotubularin-related protein-2; SBF2, SET binding factor 2; SBF1, SET binding factor 1; SH3TC2, SH3 domain and tetratricopeptide repeat domain 2; NDRG1, N-myc downstream-regulated gene 1; DNM2, Dynamin 2; GJB1, Gap junction beta-1; EGR21, Early growth response-2; HK1, Hexokinase 1; HSPB1, Heat-shock protein beta-1

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information for therapeutic targets [4]. Although four genes account for the majority (over 90%) of all CMT molecular diagnoses: peripheral myelin protein 22 (PMP22), gap junction β-1 (GJB1), myelin protein zero (MPZ), and mitofusin 2 (MFN2) [5], new genes have recently been found to be associated with CMT including PDK3 [6], GNB4 [7], INF2 [8], and FBLN5 [9,10].

Current classification of CMT depends on electrophysiological studies and patterns of inheritance. Subtypes include autosomal dominant demyelinating (CMT 1), autosomal dominant axonal (CMT 2), autosomal recessive (CMT 4) and X-linked (CMTX). Demyelinating CMT (CMT 1) is characterized by motor nerve conduction velocity (MNCV) less than 38 m/s in the forearm [11]. Dominant intermediate CMT

Table 1
CMT subtypes, genes, and protein product: function.

Disrupted process	Disease	Gene	Protein product: function
Schwann cell			
Myelin assembly	CMT1A, CMT1E, HNPP	PMP22	*Peripheral myelin protein 22*: myelin assembly
	CMT1B, CMT2I/2J, CMTDID	MPZ	*Myelin P_0 protein*: myelin assembly
Cytoskeleton	CMTDIE	INF2	*Inverted formin 2*: actin polymerization and filament severing
	CMT 4F	PRX	*Periaxin*: membrane–protein interactions stabilizing myelin sheath
	CMT 4H	FGD4	*Frabin protein*: regulates cell signaling involved in myelin production and involved in actin cytoskeleton
Channel	CMT X1	GJB1 or Cx-32	*Gap junction beta-1 or connexin-32*: gap junction formation + myelin assembly and transport
Transcription, mRNA processing	CMT 4E, CMT 1D	EGR2	*Early growth response-2*: transcription regulation
Endosomal sorting and cell signaling	CMT1C	LITAF	*Lipopolysaccharide-induced tumor necrosis factor-alpha factor*: regulation of endosome to lysosome trafficking and cell signaling
	CMT 4B1	MTMR2	*Myotubularin-related protein-2*: modifies chemical messengers, which are involved in signal transduction
	CMT4B2	SBF2	*SET binding factor 2*: development of Schwann cells
	CMT4B3	SBF1	*SET binding factor 1*: endosomal trafficking [13]
	CMT 4C	SH3TC2	*SH3 domain and tetratricopeptide repeat domain 2*: targets to intracellular endosome recycling
	CMT 4D	NDRG1	*N-myc downstream-regulated gene 1*: signaling protein shuttling between cytoplasm and nucleus
	CMT 4J	FIG4	*FIG4 protein*: abnormal transport of intracellular organelles
	CMTDIB, CMT 2M	DNM2	*Dynamin 2*: family of large GTPases and part of cell fusion–fission apparatus
Mitochondria	CMT 4G	HK1	*Hexokinase 1*: glucose metabolism
Neuron cell body and axon			
Proteasome and protein aggregation	CMT 2F	HSPB1	*Heat-shock protein beta-1*: microtubule regulator
	CMT 2L	HSPB8	*Heat-shock protein beta-8*: microtubule regulator
	CMT 2P	LRSAM1	*Leucine-rich repeat and sterile alpha motif-containing 1*: E3 ubiquitin ligase, regulates cell adhesion molecules
	CMT 2R	TRIM2	*Tripartate motif-containing protein 2*: E3 ubiquitin ligase
Cytoskeleton, axonal transport	CMT 1F, CMT 2E	NEFL2	*Neurofilament light chain*: intermediate filaments in neurons
	CMT 2O	DYNC1H1	*Dynein, cytoplasmic 1 heavy chain 1*: retrograde axonal transport
Channel	CMT 2C	TRPV4	*Transient receptor potential cation channel subfamily V member 4*: calcium homeostasis, cytoskeleton remodeling
Nuclear envelope, mRNA processing	CMTDIC	YARS	*Tyrosyl-tRNA synthetase*: aminoacyl tRNA synthetase
	CMT 2B1	LMNA	*Lamin A/C*: intermediate filament protein of nuclear envelope
	CMT 2B2	MED25	*Mediator complex subunit 25*: regulated transcription of RNA polymerase II-dependent genes
	CMT 2D	GARS	*Glycyl-tRNA synthetase*: aminoacyl tRNA synthetase
	CMT 2N	AARS	*Alanyl-tRNA synthetase*: aminoacyl tRNA synthetase
	CMT 2	MARS	*Methionyl-tRNA synthetase*: aminoacyl tRNA synthetase
	CMT 2	HINT1	*Histidine triad nucleotide binding protein 1*: modulates transcriptional activity
	CMT X5	PRPS1	*Phosphoribosyl pyrophosphate synthetase 1*: purine and pyrimidine biosynthesis
	CMTRIB	KARS	*Lysyl-tRNA synthetase*: aminoacyl tRNA synthetase
	CMT RIC	PLEKHG5	*Pleckstrin homology domain-containing protein, Family G, member 5*: nuclear factor kB-Activator
Endosomal sorting and cell signaling	CMTDIF	GNB4	*Guanine nucleotide-binding protein B4*: signal transduction
	CMT 2B	RAB7A	*Ras-related protein Rab-7*: vesicular transport and membrane traffic
	CMT 2G	TFG	*Trk-fused gene*: endoplasmic reticulum morphology
Mitochondria	CMT 2A	MFN2	*Mitofusin-2*:mitochondrial fusion
	CMT 4A, CMT2K, CMT RIA	GDAP1	*Ganglioside-induced differentiation-associated protein 1*: mitochondria fission
	CMT2Q	DHTKD1	*2-Oxoglutarate dehydrogenase E1 component*: degradation of amino acids
	CMT X4	AIFM1	*Apoptosis-inducing factor mitochondrion associated 1*: oxidative phosphorylation; apoptosis
	CMT X6	PDK3	*Pyruvate dehydrogenase kinase, isoenzyme 3*: regulates pyruvate dehydrogenase complex

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